Scientific Abstract:

Cancer is a leading cause of death in the Western World. Although most patients die from disseminated carcinoma, a substantial number die due to complications of locally advanced disease. Furthermore, patients who die of metastases frequently also suffer the morbidity of advanced local disease.

Current cancer therapy includes surgery, chemotherapy, and radiation therapy (RT). These treatment modalities, either alone or in combination, provide high degrees of local control in early stage disease but often fail in eradicating bulky tumors. The addition of gene transfer to currently available modalities provides the potential to improve control rates for these tumors.

Pancreatic cancer is one of the most lethal tumor types in the Western World. About 29,000 people are newly diagnosed with pancreatic cancer in the United States. The long-term survival from this disease remains poor with the mortality rate nearly identical with the incidence of disease and typically less than 3% of patients remain alive 5 years after the initial presentation. Curative surgical resection is most often not possible when pancreatic cancer is clinically detected because of the biologic aggressiveness of this tumor and the propensity to invade lymph, vascular, and contiguous vital structures. Combination therapy of radiation and chemotherapy is an established strategy for treatment of patients with unresectable cancer of the pancreas. These strategies improve local control and survival, but the majority of the patients will develop local recurrence and/or distant metastases and die from this disease. There has been great interest in new combination treatment strategies that improve local control, or reduce the development of metastases. The rationale for the proposed study is that the combination of external radiotherapy, Fluorouracil (5-FU) and intratumoral injection of TNFerade may improve local control, reduce regional recurrences and improve quality of life and survival as a first line therapy in adults with locally advanced pancreatic cancer.

The study will consist of an open label dose escalation phase of up to 18 patients, followed by a randomized phase with allocation of an additional 120 patients to standard therapy (5-FU and radiation) or to standard therapy plus TNFerade^{TM} biologic. Up to 18 patients will be enrolled in an open label phase to receive three escalating doses of TNFerade: 4×10^9 particle units (pu) 4×10^{10} pu, 4×10^{11} pu. If well tolerated, approximately 120 patients will be randomized to standard therapy, with or without TNFerade in a 2:1 ratio. Two doses of TNFerade will be tested: 4×10^9 pu and 4×10^{11} pu or 4×10^{10} pu, depending on the results from the dose escalation phase. If two doses of TNFerade are used, assignment to the two TNFerade groups will be double blind. Patients will be randomized to treatment groups using blocked randomization within each clinic, and stratified for maximal tumor diameter (<5 cm, ≥5 cm).

TNFerade™ biologic will be administered by direct intratumoral injection using endoscopic ultrasound (EUS)-guided fine needle injection or CT-guided percutaneous injection (CFI). The` selection of delivery method for an individual clinic will be made

according to clinical site preference. Blocked randomization by clinic will secure balance between high- and low-dose groups with regard to delivery modality. Up to three dose levels will be explored in the dose escalation phase, from $4x10^9$ particle units to $4x10^{11}$ pu in one log increments. TNFerade™ will be injected during five weekly injection sessions, concomitant with radiation. For CPI the dose will be administered as a single 2 ml injection per session. For EUS-guided injections the weekly 2 ml dose may be divided into up to four individual injections. Radiation therapy (RT) 50.4 Gy will be started on day one and administered five days weekly for a total of twenty eight 1.8 Gy fractions continued for up to 5.5 weeks. 5-FU will be administered by continuous intravenous infusion, 200 mg/m^2/day, five days a week, starting on the first day of RT and continued throughout RT.

The objective of this study is to assess the safety and potential activity of TNFerade™ in combination with 5-FU and radiation therapy for first-line treatment of unresectable locally advanced pancreatic cancer. For the safety parameters, standard clinical and laboratory function tests will be employed, including comprehensive liver function tests, tests for host immune response, and viral shedding. Also, the NCI Common Toxicity Criteria will be employed. For efficacy, the primary endpoint will be the objective tumor response rate. Secondary endpoints will include median survival, one-year survival, six-month survival, nine-month survival, time to progression (TTP), surgical down-staging and in a substudy, clinical benefit response (weight loss, performance status, pain, analgesic consumption).